Copy Sent with DEC

PCT/GB00/0028(

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BROWN, Andrew, Stephen
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
Applicant's or agent's file reference PHM 70474/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00280	**International filing date** (day/month/year) 01 February 2000 (01.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Mougamadou ABIDINE
Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM 70474/WO

Box No. I TITLE OF INVENTION

PHARMACEUTICAL COMPOSITIONS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZENECA Limited
15 Stanhope Gate
London
W1Y 6LN
GB

☐ This person is also inventor.

Telephone No.
+44-1625-516173

Facsimile No.
+44-1625-583358

Teleprinter No.
669095/669388

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

The University Court of the University of Aberdeen
Regent Walk
Aberdeen
AB24 3FX
GB

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BROWN, Andrew Stephen
Global Intellectual Property
AstraZeneca PLC
Mereside, Alderley Park, Macclesfield
Cheshire. SK10 4TG - GB

Telephone No.
+44-1625-514620

Facsimile No.
+44-1625-583358

Teleprinter No.
669095/669388

☐ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CAMERON, Norman Eugene
Diabetic Complications Laboratory
Institue of Medical Sciences
Foresterhill
Aberdeen AB25 2ZD
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COTTER, Mary Anne
Diabetic Complications Laboratory
Institute of Medical Sciences
Foresterhill
Aberdeen AB25 2ZD
GB

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus .....
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
- ☒ EE Estonia .....
- ☒ ES Spain .....
- ☒ FI Finland .....
- ☒ GB United Kingdom
- ☒ GD Grenada
- ☒ GE Georgia .....
- ☒ GH Ghana .....
- ☒ GM Gambia
- ☒ HR Croatia .....
- ☒ HU Hungary .....
- ☒ ID Indonesia
- ☒ IL Israel .....
- ☒ IN India .....
- ☒ IS Iceland
- ☒ JP Japan .....
- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakhstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ DM DOMINICA ☒ ZA SOUTH AFRICA .....
- ☒ UE UNITED ARAB EMIRATES ☒ TZ TANZANIA .....
- ☒ CR COSTA RICA ☒ MA MOROCCO .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Offic
item (1) 06Feb99 (06/02/1999)	9902591.8	GB		
item (2) 06Feb99 (06/02/1999)	9902594.2	GB		
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 17
claims	: 4
abstract	: 1
drawings	: -
sequence listing part of description	: -
Total number of sheets	: 26

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): (1) & (2)
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Brown

BROWN, Andrew Stephen
Agent for the Applicant

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

REC'D 13 FEB 2001

WIPO PCT

15

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM 70474/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00280	01/02/2000	06/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/505		
Applicant ASTRAZENECA UK AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/08/2000	09.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Economou, D Telephone No. +49 89 2399 8599

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00280

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-17 as originally filed

Claims, No.:

1-21 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-2,5,7-8,11-13,15-16.

because:

☒ the said international application, or the said claims Nos. 1-2,5,7-8,11-13,15-16 (see separate sheet, item 1) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,5,7,8,11,12,13 (see separate sheet, item 3) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10,17-20 (see separate sheet, item 5)
	No:	Claims	2-4,6,9,14-16 (see separate sheet, item 5); 21 (see separate sheet, item 4);
Inventive step (IS)	Yes:	Claims	

	No:	Claims	10,17-20 (see separate sheet, item 5)
Industrial applicability (IA)	Yes:	Claims	3-4,6,9,10,14,17-21 (see separate sheet, item 2b); 1-2,5,7-8,11-13,15-16 (see separate sheet, items 1 and 2a)
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

1). Claims 1-2,5,7-8,11-13 and 15-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2). a). For the assessment of the present claims 1-2,5,7-8,11-13 and 15-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

b). The subject-matter of claims 3-4,6,9,10,14 and 17-21 fulfils the requirements of industrial applicability.

3). The present application is directed towards the treatment of diabetic neuropathy. The subject-matter of claim 1 refers to the treatment of neuropathy in patients suffering from diabetes hence, including not solely diabetic neuropathy but also all possible forms of neuropathy (see common medical literature) which may not have diabetes as aetiology. Hence, the subject-matter of claim 1 is not supported from the description. The same applies also to claims 5,7,8,11,12 and 13 due to their dependence to claim 1.

4). From the wording of claim 21 it is not clear either the composition comprises (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or atorvastatin or (S)-2-ethoxy-3-[4-(2-{4-methansulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, or 3-{4-[2-(4-tert-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid. Pharmaceutical compositions comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or pharmaceutical salts thereof are disclosed in EP-A-0 521 471 (=**D1**; see examples 1 and 7 and claims 1-9). Hence, the subject-matter of claim 21 is not novel. The same would also apply in the light of every commercially available

atorvastatin composition.

5). EP-A-0 482 498 (**D2**) relates to a method for preventing diabetes and diabetic complications (inter alia diabetic neuropathy; see page 2, lines 12) in mammalian species by administering a cholesterol lowering drug, such as an HMG CoA reductase inhibitor, such as pravastatin, alone or in combination with an ACE inhibitor, such as captopril, zofenopril, fosinopril, enalapril, ceronapril or lisinopril (see abstract and page 2, first paragraph). The HMG CoA reductase inhibitors suitable for use include, mevastatin and related compounds, lovastatin (mevinolin) and related compounds, pravastatin and related compounds, velostatin (synvinolin) and related compounds, with lovastatin, pravastatin or velostatin being preferred. Other HMG CoA reductase inhibitors which may be employed include, fluindostatin (Sandos XU-62-320), pyrazole analogs of mevalonolactone derivatives, indene analogs of mevalonolactone derivatives, 6-[2-(substituted-pyrrol-1-yl)alkyl]-pyran-2-ones and derivatives thereof, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, 2,3-di-substituted pyrrole, furan and thiophene derivatives, naphthyl analogs of mevalonolactone, octahydro-naphthalenes, keto analogs of mevinolin (lovastatin), as well as other known HMG CoA reductase inhibitors (see page 2, lines 27-42). In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase (see page 2, line 43 to page 6, line 6). The ACE inhibitors are disclosed from page 6, line 26 to page 7, line 19). Pharmaceutical compositions and dosages are disclosed from page 7, line 21 to page 8, line 37, in the examples and in claims 2-4, 6-8,11,12-18,). In the light of **D2** the subject-matter of claims 3-4,6,9,14-16 is not novel since its technical features are already disclosed in said document.
The same applies also to claim 2 since the improvement of nerve conduction velocity is an inherent property of the statin drugs.

Any combination with a drug used for treating diabetes is obvious since the compositions are intended to be used for diabetic patients so that the subject-matter of claims 10 and 19 does not involve an inventive step.

The subject-matter of claims 17-20 (claim 20 appears twice) is formally novel

since the claimed compositions are not disclosed thus far in the available prior art.

An inventive step for the subject-matter of claims 17 and 20 (claim 20 defining combinations with lisinopril) cannot be acknowledged since combinations of HMG CoA inhibitors (the compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid already known as a HMG CoA inhibitor from **D1**; see above) with ACE inhibitors (see **D2**) are obvious combinations of the teachings of **D1** with **D2**.

Combinations of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid with AII antagonists (see claim 18 and claim 20) does also not involve an inventive step in the light of **D1** and **D2** in combination with the prior art disclosed by the applicant on page 3, lines 15 to 16).

6). Claim 20 appears twice (combination of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid with lisinopril and combination of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid with candesartan)

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/505, 31/40, 31/365, 31/22, 31/44, 31/415, A61P 43/00

A1

(11) International Publication Number: WO 00/45818

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/GB00/00280

(22) International Filing Date: 1 February 2000 (01.02.00)

(30) Priority Data:

9902591.8	6 February 1999 (06.02.99)	GB
9902594.2	6 February 1999 (06.02.99)	GB

(71) Applicants *(for all designated States except US)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). THE UNIVERSITY COURT OF THE UNIVERSITY OF ABERDEEN [GB/GB]; Regent Walk, Aberdeen AB24 3FX (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CAMERON, Norman, Eugene [GB/GB]; Institute of Medical Sciences, Diabetic Complications Laboratory, Foresterhill, Aberdeen AB25 2ZD (GB). COTTER, Mary, Anne [GB/GB]; Institute of Medical Sciences, Diabetic Complications Laboratory, Foresterhill, Aberdeen AB25 2ZD (GB).

(74) Agent: BROWN, Andrew, Stephen; AstraZeneca UK Limited, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF 3–HYDROXY–3–METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

(57) Abstract

The present invention relates to a new use of a statin drug in the improvement of diabetic neuropathy, specifically in improving nerve conduction velocity and nerve blood flow in patients suffering diabetes, in particular to pharmaceutical combinations of the statin drug and other agents known to improve diabetic neuropathy such as an aldose reductase inhibitor (ARI), an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II (AII) antagonist which combinations are useful in the prevention and treatment of the complications of diabetes.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

The present invention relates to a new use of a statin drug in the improvement of diabetic neuropathy, specifically in improving nerve conduction velocity and nerve blood flow in patients suffering diabetes, in particular to pharmaceutical combinations of the statin drug and other agents known to improve diabetic neuropathy such as an aldose reductase inhibitor (ARI), an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II (AII) antagonist which combinations are useful in the prevention and treatment of the complications of diabetes.

3-Hydroxy-3-methylglutaryl Coenzyme A (HMG Co A) reductase inhibitors effectively inhibit cholesterol synthesis in the liver through stimulation of the low density lipoprotein (LDL) receptors. These drugs are currently pre-eminent in the treatment of all hypercholesterolaemia, except the relatively rarely occurring homozygous familial hypercholesterolaemia. Therapy with HMG Co A-reductase inhibitors may result in regression of atherosclerotic vascular lesions and several HMG Co A-reductase inhibitors have proven to reduce mortality. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

We have discovered that statin drugs, in particular (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the AGENT), the calcium salt of which is shown in Fig. 1 below, and atorvastatin produce an improvement in the nerve conduction velocity (NCV) and nerve blood flow in an animal model of diabetic neuropathy. Therefore, statin drugs may be used to improve diabetic neuropathy, whether in type I or type II diabetes.

Therefore we present as a first feature of the invention a method for treating neuropathy in a patient suffering from diabetes comprising administering to the patient a statin drug.

As a preferred feature of the invention we present a method for improving nerve conduction velocity and /or nerve blood flow in a patient suffering diabetic neuropathy comprising administering to the patient a statin drug.

Further features of the invention include use of a statin drug in the preparation of a medicament for use in the treatment of any of the conditions mentioned above.

Examples of statin drugs include, for example, pravastatin (PRAVACHOL™), lovastatin (MEVACOR™), simvastatin (ZOCOR™), cerivastatin (LIPOBAY™), fluvastatin (LESCOL™), atorvastatin (LIPITOR™) and the AGENT, the structures of which are shown in Figure 1. Preferably the statin drug is atorvastatin or the AGENT. Preferably the AGENT is used at a dose of 5 to 80 mg per day.

The AGENT is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase). Preferably the calcium salt is used as illustrated in Figure 1.

Atorvastatin is disclosed in US 5,273,995; lovastatin is disclosed in US 4,231,938; simvastatin is disclosed US 4,450,171 and US 4,346,227; pravastatin is disclosed in US 4,346,227; fluvastatin is disclosed in US 4,739,073; cerivastatin is disclosed in US 5,177,080 and US 5,006,530.

Other compounds which have inhibitory activity against HMG-CoA reductase can be readily identified by using assays well known in the art. Examples of such assays are disclosed in US 4,231,938 at column 6 and WO84/02131 at pages 30-33.

It will be appreciated that the statin drug may be administered in accordance with the invention in combination with other drugs used for treating diabetes or the complications of diabetes, such as neuropathy, nephropathy, retinopathy and cataracts. Examples of such treatments include insulin sensitising agents, insulin and oral hypoglycaemics (these are

divided into four classes of drug - sulfonylureas, biguanides, prandial glucose regulators and alpha-glucosidase inhibitors). Examples of insulin sensitising agents include, for example, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid. Examples of sulfonylureas are glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide. An example of a biguanide is metformin. An example of an alpha-glucosidase inhibitor is acarbose. An example of a prandial glucose regulator is repaglinide.

Other treatments are known also to improve NCV in diabetic neuropathy and as such these represent preferred combinations of the invention. Examples of such treatments include aldose reductase inhibitors, ACE inhibitors and AII antagonists.

The use of aldose reductase inhibitors or ACE inhibitors in improving NCV and treating diabetic neuropathy is disclosed in PCT/GB98/01959. The use of AII antagonists in improving NCV and treating diabetic neuropathy is disclosed in WO93/20816.

Suitable aldose reductase inhibitors include, for example, epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509).

Suitable ACE inhibitors include, for example, benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, and cilazapril. A preferred ACE inhibitor includes, for example, lisinopril, or a pharmaceutically acceptable salt thereof.

Suitable AII antagonists include, for example, losartan, irbesartan, valsartan and candesartan. A preferred AII antagonist is candesartan.

Independent aspects of the present invention include a pharmaceutical combination comprising any one of the statin drugs identified above, preferably the AGENT or atorvastatin, and any one of the named ACE inhibitors identified above, or anyone of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above. Accordingly, further independent aspects of the present invention include the following:

(1) A pharmaceutical combination comprising the AGENT and lisinopril;

(2) A pharmaceutical combination comprising atorvastatin and lisinopril;

(3) A pharmaceutical combination comprising fluvastatin and lisinopril;

(4) A pharmaceutical combination comprising pravastatin and lisinopril;

(5) A pharmaceutical combination comprising cerivastatin and lisinopril;

(6) A pharmaceutical combination comprising the AGENT and candesartan;

(7) A pharmaceutical combination comprising the AGENT, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

The 'pharmaceutical combination' may be achieved by dosing each component drug of the combination to the patient separately in individual dosage forms administered together or sequentially. Alternatively the 'pharmaceutical combination' may be together in the same unit dosage form.

Therefore, as a further aspect of the invention we represent a pharmaceutical composition comprising a pharmaceutical combination as described herein above together with a pharmaceutically acceptable carrier and/or diluent.

Independent aspects of the present invention include a pharmaceutical composition comprising any one of the statin drugs identified above, preferably the AGENT or atorvastatin, and any one of the named ACE inhibitors identified above, or any one of the aldose reductase inhibitors identified above, or any one of the AII antagonists identified above together with a pharmaceutically acceptable carrier and/or diluent. Accordingly, further independent aspects of the present invention include the following:

(1) A pharmaceutical composition comprising the AGENT and lisinopril;

(2) A pharmaceutical composition comprising atorvastatin and lisinopril;

(3) A pharmaceutical composition comprising fluvastatin and lisinopril;

(4) A pharmaceutical composition comprising pravastatin and lisinopril;

(5) A pharmaceutical composition comprising cerivastatin and lisinopril;

(6) A pharmaceutical composition comprising AGENT and candesartan; and

(7) A pharmaceutical composition comprising the AGENT, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid; and

together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an ACE inhibitor (including any one of the ACE inhibitors specifically named above, in particular lisinopril), together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an aldose reductase inhibitor (including any one specifically named above), together with a pharmaceutically acceptable carrier and/or diluent.

A preferred pharmaceutical composition of the invention comprises the AGENT or atorvastatin and an AII antagonist (including any one specifically named above and preferably candesartan), together with a pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical compositions of the present invention may be administered in a standard manner for example by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred.

The dose of a statin drug, an aldose reductase inhibitor, an AII antagonist or an ACE inhibitor which can be administered in accordance with the present invention depends on several factors, for example the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen and the desired result, and additionally the potency of the statin drug, aldose reductase inhibitor, AII antagonist and ACE inhibitor employed in the composition. In addition, account should be taken of the recommended maximum daily dosages for the ACE inhibitors.

Prolonged administration of an ACE inhibitor at a therapeutically effective dose may be deleterious or give rise to side effects in certain patients, for example it may lead to significant deterioration of renal function, induce hyperkalemia, neutropenia, angioneurotic oedema, rash or diarrhoea or give rise to a dry cough. Administration of an ARI may also give rise to deleterious effects or side effects at the dose required to inhibit the enzyme aldose reductase sufficiently to produce a significant beneficial therapeutic effect. The present invention lessens the problems associated with administration of an ARI or an ACE inhibitor alone

and/or provides a means for obtaining a therapeutic effect which is significantly greater than that otherwise obtainable with the single agents when administered alone. Furthermore, diabetic neuropathy involve a complex mechanism or number of mechanisms, which initiate a cascade of biochemical alterations that in turn lead to structural changes. These may result in a diverse patient population. The present invention therefore provides the additional advantage that it allows tailoring of treatment to the needs of a particular patient population.

The combination of a statin, preferably atorvastatin or the AGENT, with and ACE inhibitor, preferably lisinopril, is either additive or synergistic in effect in the treatment of neuropathy, in particular NCV or nerve blood flow, in diabetic pateients.

The combination of a statin, preferably atorvastatin or the AGENT, with and AII antagonist, preferably candesartan, is either additive or synergistic in effect in the treatment of neuropathy, in particular NCV or nerve blood flow, in diabetic pateients.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 100 mg of the statin drug, or/and from 0.1 mg to 500 mg of an aldose reductase inhibitor, or/and from 0.1 mg to 500 mg of an ACE inhibitor. Preferably a unit dose formulation will contain 5 to 80 mg of the statin drug, or/and 0.1 to 100 mg of an aldose reductase inhibitor, or/and 0.1 mg to 100 mg of an AII antagonist or/and 0.1 to 100 mg of an ACE inhibitor.

The present invention covers the pharmaceutical combination of (or product containing) the statin and an aldose reductase inhibitor, an AII antagonist or an ACE inhibitor for simultaneous, separate or sequential use in the treatment of diabetic neuropathy. In one aspect of the present invention, the AGENT drug and the aldose reductase inhibitor or AII antagonist or ACE inhibitor is presented in admixture in one pharmaceutical dosage form. In another aspect, the present invention covers the administration of separate unit dosages of the AGENT and aldose reductase inhibitor or AII antagonist or ACE inhibitor in order to achieve the desired therapeutic effect. Such separate unit dosages may be administered concurrently or sequentially as determined by the clinician. The present invention also covers an agent for

the treatment of diabetic neuropathy comprising a pharmaceutically acceptable carrier and/or diluent and, as active agents, a statin drug, preferably the AGENT or atorvastatin, and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in quantities producing a synergistic therapeutic effect.

In another aspect of the invention there is provided a combination of pharmaceutical compositions for combination therapy of diabetic neuropathy, the combination consisting of a pharmaceutical composition comprising the statin drug and a pharmaceutical composition comprising an aldose reductase inhibitor or a pharmaceutical composition comprising an AII antagonist or a pharmaceutical composition comprising an ACE inhibitor.

A further aspect of the present invention comprises the use of a statin drug and an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor in the preparation of a pharmaceutical composition for use in the treatment of diabetic neuropathy.

A further aspect of the present invention is a method for treating diabetic neuropathy wherein a therapeutically effective amount of a statin drug in combination with an aldose reductase inhibitor or an AII antagonist or an ACE inhibitor is administered systemically, such as orally or parenterally. Where the patient to be treated is normotensive, the ACE inhibitor or AII antagonist will preferably be administered in amounts below that required to cause a reduction in blood pressure. Where the patient to be treated is hypertensive, the ACE inhibitor or AII antagonist will preferably be used in amounts usually employed to treat hypertension.

The effect of a pharmaceutical composition of the present invention may be examined by using one or more of the published models of diabetic neuropathy well known in the art. The pharmaceutical compositions of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, deficits in nerve function found in diabetic patients, and therefore particularly useful in the treatment of diabetic neuropathy. This may be demonstrated, for example, by measuring markers such as nerve conduction velocity, nerve blood flow, nerve evoked potential amplitude, quantitative sensory testing, autonomic function testing and morphometric changes. Experimentally, studies analogous to those

described in Diabetologia, 1992, Vol. 35, pages 12-18 and 1994, Vol. 37, pages 651-663 may be carried out.

A further aspect of the present invention is a method of treating or preventing the development of disease conditions associated with impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment comprising administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

A further aspect of the present invention is a method of reversing impaired neuronal conduction velocity in a warm-blooded animal (including a human being) requiring such treatment comprising administering to said animal a therapeutically effective amount of a pharmaceutical combination or composition as described above.

Dosages of the AGENT may be administered according to the cholesterol lowering effect desired from a range of 5-80 mg per day in any number of unit dosages.

Suitable dosages of the statins, ACE inhibitors, aldose reductase inhibitors or AII antagonists mentioned herein are those which are available commercially, and which may be further reduced as suggested herein, or as advised in such publications as Monthly Index of Medical Specialities (P.O.BOX 43, Ruislip, Middlesex, UK).

The following non-limiting Examples serve to illustrate the present invention.

Example 1

Suitable pharmaceutical compositions of an aldose reductase inhibitor (ARI) include the following:

Tablet 1

	mg/tablet
ARI	100
Lactose Ph. Eur.	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

Tablet 2

ARI	50
Lactose Ph.Eur.	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

Tablet 3

ARI	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

Capsule 1

ARI	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

Example 2

Suitable pharmaceutical compositions of an ACE inhibitor include the following:

Tablet 1

ACE Inhibitor	100
Corn starch	50
Gelatin	7.5
Microcrystalline cellulose	25
Magnesium stearate	2.5

Tablet 2

ACE inhibitor	20
Pregelatinised starch	82
Microcrystalline cellulose	82
Magnesium stearate	1

Example 3

Capsule	mg
The AGENT	5.0
Lactose	42.5
Corn starch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3
Hydrotalcite	1.1
Magnesium stearate	1.1

Capsules containing 1, 2.5 or 10mg of the Agent may be obtained similarly using more or less lactose as appropriate., to achieve a fill weight of 105mg.

Example 4

Suitable pharmaceutical compositions containing the AGENT and an ACE inhibitor in a single dosage form include the following:

Capsule	mg
The AGENT	5.0
Lisinopril	10.0
Lactose	42.5
Corn starch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3
Hydrotalcite	1.1
Magnesium stearate	1.1

Example 5

A patient requiring treatment for diabetic neuropathy is treated with the AGENT (10 mg) and lisinopril (10 mg). Lisinopril is administered twice daily and the AGENT is administered once daily.

Example 6

Male Sprague-Dawley rats, 19 weeks old at the start of the study, were divided into non-diabetic animals (normal control group) and animals rendered diabetic by intraperitoneal administration of streptozotocin, (40 - 45 mg/kg, freshly dissolved in sterile saline). Diabetes was verified 24 hours later by estimating hyperglycaemia and glucosuria (Visidex II and Diastix; Ames, Slough, UK). Diabetic rats were tested weekly and weighed daily. Animals were rejected if the plasma glucose concentration was < 20 mM of if body weight consistently increased over 3 days. Samples were taken from the tail vein or carotid artery after final experiments for plasma glucose determination (GOD-Perid method; Boehringer

Mannheim, Mannheim, Germany). After 6 weeks of untreated diabetes, groups of rats were treated for a further 2 weeks with the AGENT, dissolved in the drinking water.

At the end of the treatment period, rats were anaesthetised with thiobutabarbitone by intraperitoneal injection (50 - 100 mg/kg). The trachea was cannulated for artificial ventilation and a carotid cannula was used to monitor mean systemic blood pressure.

Motor nerve conduction velocity was measured (as previously described by Cameron et al, Diabetologia, 1993, Vol. 36, pages 299-304) between sciatic notch and knee in the nerve branch to tibialis anterior muscle, which is representative of the whole sciatic nerve in terms of susceptibility to diabetes and treatment effects.

Sensory conduction velocity in saphenous nerve was measured between the groin and ankle (as previously described by Cameron et al. Quarterly Journal of Experimental Physiology, 1989, vol. 74, pages 917-926).

Sciatic blood flow was measured by hydrogen clearance microelectrode polarography (as described by Cameron et al., Diabetologia, 1994, vol.37, pages 651-663). The nerve was exposed between the sciatic notch and the knee and the skin around the incision was sutured to a metal ring to form a pool that was filled with paraffin oil that was maintained at 35-37°C by radiant heat. A glass-insulated platinum micro-electrode was inserted into the middle portion of the sciatic nerve and polarised at 250mV with respect to a subcutaneous reference microelectrode. 10%Hydrogen was added to the inspired gas, the proportions of nitrogen and oxygen being adjusted to 70% and 20% respectively. When the hydrogen current recorded by the electrode had stabilised, indicating equilibrium with arterial blood, the hydrogen supply was shut off and nitrogen supply was increased appropriately. The hydrogen clearance curve was recorded until a baseline, defined as no systematic decline in electrode current over 5 minutes. To estimate blood flow , clearance curves were digitised and exponential curves were fitted to the data by computer using non-linear regression. The best fitting exponent gave a measure of nerve blood flow.

Data

All data expressed as group mean ± SEM (number of rats used in brackets)

Sciatic Nerve Motor Conduction Velocity

Control Values

Non-diabetical control	64.04 ± 0.46 (10)
8 week diabetic + vehicle	50.35 ± 0.93 (6)

Atorvastatin

9Diabetic + 2 weeks of dosing at 20mg/kg	61.53 ± 0.76 (6)
Diabetic + 2 weeks of dosing at 50mg/kg	63.59 ± 0.69 (6)

The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	63.34 ± 0.61 (8)

Dose response determination 5 groups of 8 rats - dose ranged from 0.3-20mg/kg - ED_{50} = 2.3mg/kg

Saphenous Nerve Sensory Conduction Velocity

Control Values

Non-diabetic control	61.09 m/s ± 0.67 (10)
8 week diabetic + vehicle	52.77 m/s ± 0.79 (6)

Atorvastatin

Diabetic + 2 weeks of dosing at 20mg/kg	59.77 m/s ± 0.93 (6)
Diabetic + 2 weeks of dosing at 50mg/kg	60.72 m/s ± 0.94 (6)

The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	60.57 m/s ± 0.83 (8)

Dose response determination 5 groups of 8 rats - dose ranged from 0.3-20mg/kg - ED_{50} = 0.9mg/kg

Sciatic Nerve Blood Flow

Control Values

Non-diabetic control	17.89 ml/min/100g (of nerve tissue) ± 0.65 (10)
8 week diabetic + vehicle	8.82 ml/min/100g ± 0.56 (10)

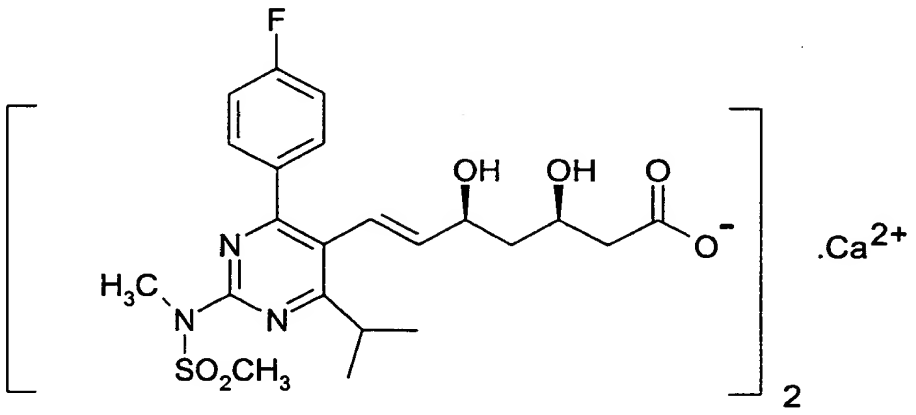
Atorvastatin

Diabetic + 2 weeks of dosing at 50mg/kg	16.96 ± 1.39 ml/min/100g (6)

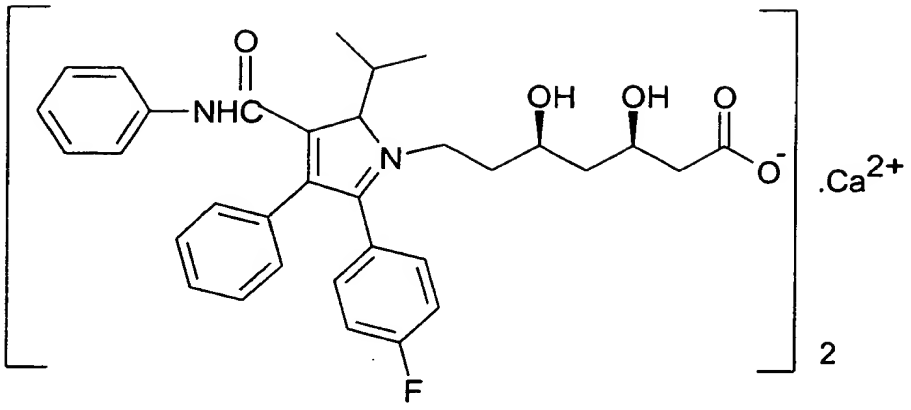
The AGENT

Diabetic + 2 weeks of dosing at 20mg/kg	16.19 ± 0.51 ml/min/100g (8)

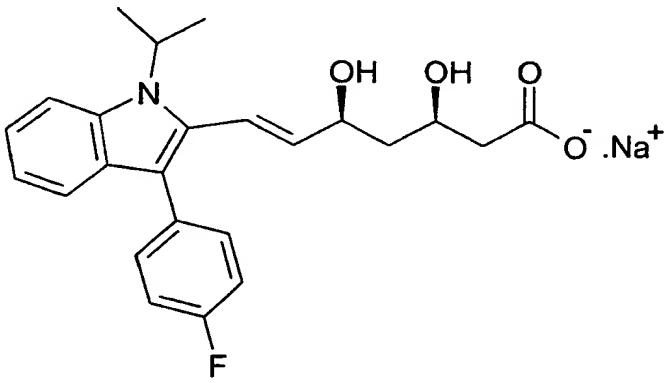
Figure 1.



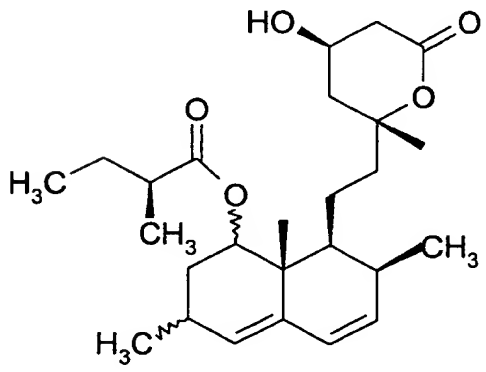
The AGENT



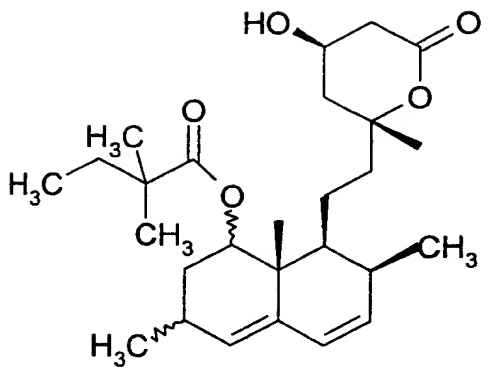
Atorvastatin



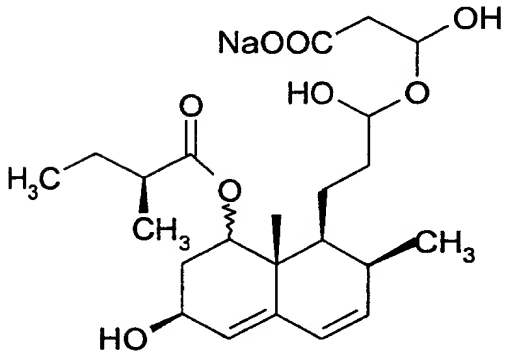
Fluvastatin



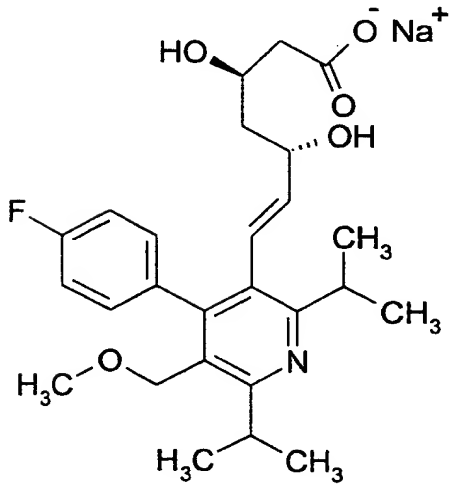
Lovastatin



Simvastatin



Pravastatin



Cerivastatin

Claims

1. A method for treating neuropathy in patients suffering from diabetes comprising administering to the patient a statin drug.

2. A method for improving nerve conduction velocity or nerve blood flow in a patient suffering diabetic neuropathy comprising administering to the patient a statin drug.

3. Use of a statin drug in the preparation of a medicament for use in the treatment of diabetic neuropathy.

4. Use of a statin drug in the preparation of a medicament for use in the improvement of nerve conduction velocity or nerve blood flow in a patient having diabetic neuropathy.

5. A method as claimed in either claim 1 or claim 2 wherein the statin drug is selected from pravastatin, simvastatin, cerivastatin, fluvastatin, atorvastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

6. Use as claimed in either claim 3 or claim 4 wherein the statin drug is selected from pravastatin, simvastatin, cerivastatin, fluvastatin, atorvastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

7. A method as claimed in claim 1, 2 or 5 wherein the statin drug is used in combination with at least one other drug used for treating diabetes or the complications of diabetes.

8. A method as claimed in claim 7 wherein the drug used for treating diabetes or the complications of diabetes is selected from insulin, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic

acid, glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide, metformin, acarbose and repaglinide.

9. Use as claimed in claim 3, 4 or 6 wherein the statin drug is used in combination with at least one other drug used for treating diabetes or the complications of diabetes.

10. Use as claimed in claim 9 wherein the drug used for treating diabetes or the complications of diabetes is selected from insulin, troglitazone, rosiglitazone, pioglitazone, MCC-555, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, glimepiride, glibenclamide, gliclazide, glipizide, gliquidone and tolazamide, metformin, acarbose and repaglinide.

11. A method as claimed in claim 2 or 5 wherein the statin drug is used in combination with a second drug which is also useful in improving nerve conduction velocity in a patient suffering diabetic neuropathy.

12. A method as claimed in claim 11 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitors and an AII antagonist.

13. A method as claimed in claim 12 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

14. Use as claimed in either claim 3 or 6 wherein the statin drug is used in combination with a second drug which is also useful in improving nerve conduction velocity in a patient suffering diabetic neuropathy.

15. A method as claimed in claim 14 wherein the second drug is selected from an aldose reductase inhibitor, an ACE inhibitors and an AII antagonist.

16. A method as claimed in claim 15 wherein the second drug is selected from epalrestat, tolrestat, ponolrestat, zopolrestat, AD-5467, SNK-860, ADN-138, AS-3201, zenarestat, sorbinil, methosorbinil, imirestat and minalrestat (WAY-121509), benazepril, benazeprilat, captopril, delapril, fentiapril, fosinopril, imidopril, libenzapril, moexipril, pentopril, perindopril, pivopril, quinapril, quinaprilat, ramipril, spirapril, spiraprilat, trandolapril, zofenopril, ceronapril, enalapril, indolapril, lisinopril, alacepril, cilazapril, losartan, irbesartan, valsartan and candesartan.

17. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and lisinopril.

18. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and candesartan.

19. A pharmaceutical combination comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, or atorvastatin, and (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid

20. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, lisinopril and a pharmaceutically acceptable diluent or carrier.

21. A pharmaceutical composition comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, or atorvastatin, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, and a pharmaceutically acceptable carrier or diluent.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PHM 70474/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/00280	01/02/2000	06/02/1999
Applicant		
ZENECA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF 3-HYDROXY-3-METHYLGLUTARYL COENZYM A REDUCTASE INHIBITORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DIABETIC NEUROPATHY

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 00/00280

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/40 A61K31/365 A61K31/22 A61K31/44
A61K31/415 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 521 471 A (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 7 January 1993 (1993-01-07) cited in the application examples 1,7 claims 1-9	21
X	US 5 130 333 A (E.R.SQUIBB & SONS, INC.) 14 July 1992 (1992-07-14) abstract column 4, line 27 -column 13, line 15 claims 1,2	1-21
X	EP 0 482 498 A (E.R.SQUIBB & SONS, INC.) 29 April 1992 (1992-04-29) the whole document page 2, line 10 - line 12	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	29/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 00/00280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0521471 A	07-01-1993	CA 2072945 A	02-01-1993
		HU 61531 A	28-01-1993
		JP 2648897 B	03-09-1997
		JP 5178841 A	20-07-1993
		KR 9605951 B	06-05-1996
		US 5260440 A	09-11-1993
US 5130333 A	14-07-1992	US 5190970 A	02-03-1993
EP 0482498 A	29-04-1992	CA 2052014 A	20-04-1992
		JP 4282324 A	07-10-1992

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 October 2000 (03.10.00)	
International application No. PCT/GB00/00280	**Applicant's or agent's file reference** PHM 70474/WO
International filing date (day/month/year) 01 February 2000 (01.02.00)	**Priority date** (day/month/year) 06 February 1999 (06.02.99)
Applicant CAMERON, Norman, Eugene et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 August 2000 (30.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PA NT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BROWN, Andrew, Stephen
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
Applicant's or agent's file reference PHM 70474/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00280	**International filing date** (day/month/year) 01 February 2000 (01.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Mougamadou ABIDINE
Telephone No.: (41-22) 338.83.38

PA NT COOPERATION TREAT

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BROWN, Andrew, Stephen
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
Applicant's or agent's file reference PHM 70474/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00280	**International filing date** (day/month/year) 01 February 2000 (01.02.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

BROWN, Andrew, Stephen
AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 44 1625 514620

Facsimile No.: 44 1625 583358

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

BROWN, Andrew, Stephen
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield, Cheshire SK10 4GR
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 44 1625 514620

Facsimile No.: 44 1625 583358

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Mougamadou ABIDINE

Telephone No.: (41-22) 338.83.38